REMARKS

I. Status of the Claims.

Prior to amendment, Claims 1-5 were present in the application and stand rejected. By the foregoing amendments, Claim 1 has been amended to incorporate the limitations of Claims 4 and 5. Claim 2 has been amended to specify identifying an invasive microbial population of the eye, in accordance with Claim 1, and to include identifying an antifungal of Claim 5 capable of inhibiting the invasive microbial population. Claim 3 has been amended to incorporate the limitations of amended Claim 1. Claim 5 has been amended to include the pharmaceutically acceptable salts of the recited antifungal agents. It is believed that Claims 1-5 are in condition for allowance in view of the foregoing amendments and following comments. Reconsideration and favorable action is requested.

Rejection of Claims 1-5 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Holly et al. (US 5,380,303) in view of Ritchie et al. (US 2004/0151765). According to the Examiner, Holly et al. teaches the use of an antimicrobial agent in combination with a chelating agent such as EDTA and a buffer in an ophthalmic formulation. According to the Examiner, Holly et al. differs from the claimed invention in the presence of the specific antibiotics and antifungal agents in the dependent claims. The Examiner has cited Ritchie et al. US 2004/0151765 as teaching the use of the claimed antibiotics (citing page 4, Column 2, paragraph [0050]) in combination with EDTA (citing page 4, Column 1, paragraph [0047]) for the treatment of microbial infection and wound healing (citing the abstract). In the Examiner's view, the cited references in combination make it clear that the claimed antibiotics have been previously used in combination with EDTA. According to the Examiner, to prepare a suitable ophthalmic formulation would have been obvious to a person in the art, considering that Holly et

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al. teaches the use of EDTA and an antimicrobial agent in ophthalmic formulations as old and well known. This rejection is respectfully traversed.

II. The Obviousness Rejection Is Overcome.

When assessing the patentability of a claim, the Supreme Court in *KSR* confirmed that the *Graham* Factor Analyses should be used with respect to obvious determinations under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). Therefore, the following subsections set forth the rejected claims, the scope and content of the cited art and the differences between the rejected claims and the cited art, and an explanation as to why these differences are not rendered obvious. As will be explained, Holly et al. in view of Ritchie et al. neither teaches nor suggests a method of inhibiting a microbial infection of an eye comprising contacting an eye of a human or animal patient with an amount of a composition effective for promoting wound healing, the composition comprising from 1 mM to 250 mM of ethylenediaminetetraacetic acid (EDTA), from 5 mM to 250 mM of Tris (hydroxymethyl) aminomethane, a pharmaceutically acceptable antibiotic or antifungal selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols, tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins, Gramicidins, itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, as required by amended Claim 1. Further, Holly et al. in view of Ritchie et al. neither teaches nor suggests identifying an invasive microbial population of the eye, identifying an antibiotic capable of inhibiting the proliferation of the invasive microbial population, determining the MIC and FIC values for the antibiotic or antifungal and the chelating agent; and adjusting the concentration of

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the antibiotic or antifungal and the chelating agent of the antimicrobial composition to inhibit the proliferation of the microbial population, as required by amended Claim 2; the kits of amended Claim 3; the method of Claim 1 wherein the antibiotic or antifungal is an antibiotic selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols, tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins and Gramicidins, or a pharmaceutically acceptable salt thereof, as required by Claim 4; or the method of Claim 1 wherein the antibiotic or antifungal is an antifungal selected from the group consisting of itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate, or a pharmaceutically acceptable salt thereof, as required by Claim 5. For at least these reasons, the obviousness rejection is improper.

A. Scope and Content of the Rejected Claims.

Claim 1, as amended, is directed to a method of inhibiting a microbial infection of an eye comprising contacting an eye of a human or animal patient with an amount of a composition effective for promoting wound healing, the composition comprising from 1 mM to 250 mM of ethylenediaminetetraacetic acid (EDTA), from 5 mM to 250 mM of Tris (hydroxymethyl) aminomethane, a pharmaceutically acceptable antibiotic or antifungal selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols, tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins, Gramicidins, itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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Claims 2, 4, and 5 depend from Claim 1. Claim 2 further requires identifying an invasive microbial population of the eye, identifying an antibiotic or antifungal capable of inhibiting the proliferation of the invasive microbial population, determining the MIC and FIC values for the antibiotic or antifungal and the chelating agent, and adjusting the concentration of the antibiotic and the chelating agent of the antimicrobial composition to inhibit the proliferation of the microbial population.

Claim 3 is directed to a kit for managing an eye infection of an animal or human patient comprising an amount of a composition of Claim 1 effective for promoting wound healing, and instructions for using the composition.

Claim 4 requires that the antibiotic or antifungal is an antibiotic selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols, tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins and Gramicidins, or a pharmaceutically acceptable salt thereof.

Claim 5 requires that the antibiotic or antifungal is an antifungal selected from the group consisting of itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate, or a pharmaceutically acceptable salt thereof.

B. The Scope and Content of the Cited Art and the Differences Between the Cited Art and the Rejected Claims.

As previously explained, Holly et al. US 5,380,303 relates specifically to the use of a known industrial polymeric antimicrobial agent, poly[oxyethylene(dimethylimino)-ethylene-(dimethylimino)ethylene dichloride] in a pharmaceutical preparation in combination with a buffer and metal ion chelating agent for application to ophthalmic solutions for disinfecting contact lenses and preserving ocular solutions used to treat contact lenses and ocular disease (see

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Column 4, lines 48-55). The Holly et al. '303 patent teaches directly away from using small molecule antibiotics and antifungals in the disclosed composition. As disclosed in the Holly et al. '303 patent at Column 2, lines 35-47:

> The monomeric antibacterial agents listed earlier ["Polyquad" or alpha-4[1-tris(2-hydroxyethyl) ammonium chloride-2-dibutenyl] poly[1-dimethyl ammonium chloride-2-dibutenyl]-.omega.-tris (2-hydroxyethyl) ammonium chloride, and "Dymed" or poly[aminopropyl-bis(biguanide)] or poly[hexamethylene-bis(biguanide)]] cannot be added to ophthalmic formulations likely to be used by patients who wear hydrogel contact lenses because the small molecular size of these agents enable them to penetrate pores of hydrogels, the polymeric matrices of the hydrogel materials. The antimicrobial agent accumulated within the lens matrix would eventually leach into the tear film upon application of the lens to the eye. The pore size in poly(hydroxyethylmethacrylate) [poly(HEMA)] gels used in the fabrication of hydrogel lenses is approximately 30-50 Angstroms, as reported in Hydrogels in Medicine and Pharmacy, Vol. II, Polymers. Ed. Peppas, N. K., CRC Press, Inc.

Accordingly, the Holly et al. '303 patent teaches away from the use of small molecule antibiotics or antifungals in its ophthalmic solutions, and specifically does not disclose or remotely suggest inhibiting a microbial infection of an eye by contacting an eye of a patient with a composition comprising from 1 mM to 250 mM of ethylenediaminetetraacetic acid (EDTA), from 5 mM to 250 mM of Tris (hydroxymethyl) aminomethane, a pharmaceutically acceptable antibiotic or antifungal selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols, tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins, Gramicidins, itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, as claimed in applicants' amended claims.

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Ritchie et al. US 2004/0151765 discloses methods and composition methods for wound management that comprise contacting a wound of a patient with an effective amount of a therapeutic composition comprising a chelating agent, a pH buffering agent, an antimicrobial agent, Vitamin E and a carrier and a surfactant. As set forth above, the Examiner has cited Ritchie et al. as teaching the use of the antibiotics of the present claims (citing page 4, Column 2 paragraph [0050]) in combination with EDTA (citing page 4, Column 1, paragraph [0047]) for the treatment of microbial infection and wound healing. In the relevant portion of Ritchie et al. relied on by the Examiner, Ritchie et al. discloses at paragraph [0050]:

> [0050] . . . Antibiotics suitable for use in the wound management methods of the present invention include, but are not limited to, β-lactams (penicillins and cephalosporins), vancomycins, bacitracins, macrolides (erythromycins), lincosamides (clindomycin), chloramphenicols, tetracyclines, aminoglycosides (gentamicins), amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides and trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins and Gramicidins and the like and any salts or variants thereof. It also understood that it is within the scope of the present invention that the tetracyclines include, but are not limited to, immunocycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline and minocycline and the like. It is also further understood that it is within the scope of the present invention that aminoglycoside antibiotics include, but are not limited to, gentamicin, amikacin and neomycin and the like.

At paragraph [0047], Ritchie et al. discloses that the pharmaceutically acceptable chelating agent may be EDTA, and the chelating agent, when delivered to a wound of a human or animal patient will have a concentration between from about 1mM to about 250 mM, more preferably from about 1 mM to about 100 mM, most preferably from about 1 mM to about 50 mM.

C. The Differences Between the Cited Art and the Rejected Claims are not Obvious Differences.

In the context of an obviousness rejection, the Supreme Court explained the importance of "identify[ing] a reason" why a skilled artisan would be prompted to arrive at the presently

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claimed invention. *KSR*, 127 S. Ct. at 1741. The Court noted that there should be an "explicit" analysis regarding "whether there was **an apparent reason** to combine the known elements **in the fashion claimed** by the patent at issue." *Id.* (emphasis added). As will be explained, there is no apparent reason to modify Holly et al. to arrive at the presently claimed invention because this reference teaches directly away from incorporation of the small molecule antibiotics and antifungals disclosed by Ritchie et al. US 2004/0151765.

1. Holly et al. in View of Ritchie et al. Fails to Teach or Suggest All Elements of Amended Claim 1.

KSR did not change the requirement that to support an obviousness rejection, a reference, alone or in combination, must teach or suggest every element of a claimed invention. For example, the Board of Patent Appeals and Interferences recently confirmed that a proper obviousness determination requires that an examiner make "a searching comparison of the claimed invention - *including all its limitations* - with the teaching of the prior art." *Ex parte Competitive Technologies, Inc.*, Appeal 2009-005519 (citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995)) (emphasis added). Citing the *KSR* decision, Section 2143.02 of the M.P.E.P. similarly states, "A rationale to support a conclusion that a claim would have been obvious is that ***all the claimed elements were known in the prior art***..." (emphasis added - internal citation omitted).

With respect to amended Claim 1, the Examiner has failed to show that Holly et al. in view of Ritchie et al. teaches or suggests "a method of inhibiting a microbial infection of an eye comprising contacting an eye of a human or animal patient with an amount of a composition effective for promoting wound healing, the composition comprising from 1 mM to 250 mM of ethylenediaminetetraacetic acid (EDTA), from 5 mM to 250 mM of Tris (hydroxymethyl) aminomethane, a pharmaceutically acceptable antibiotic or antifungal selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols,

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tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins, Gramicidins, itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier" as required by applicants' Claim 1. *See* M.P.E.P. § 2142 (an examiner bears the initial burden of factually supporting any *prima facie* case of obviousness).

Although, Holly et al. teaches the use of a known industrial polymeric antimicrobial agent, poly[oxyethylene(dimethylimino)-ethylene-(dimethylimino)ethylene dichloride] in an ophthalmic preparation, this reference teaches directly away from incorporation of the small molecule antibiotics of Ritchie et al., as described above. Accordingly, a person of ordinary skill in the art would be led away from the combination of portions of these references as cited by the Examiner. In addition, neither Holly et al. nor Ritchie et al. teaches the use of the recited antifungals in the treatment of eye infections, as recited in applicants' claims.

Because Holley et al. in view of Ritchie et al. fails to teach or suggest all elements of Claim 1, a skilled artisan would not have an apparent reason to modify Holly et al. with the cited antibiotics of Ritchie et al. to arrive at the claimed invention. *See KSR*, 127 S. Ct. at 1741. For at least this reason, the obviousness rejection of Claim 1 is improper.

2. Holley et al. in View of Ritchie et al. Fails to Teach or Suggest All Elements of Claims 2-5.

Not only does Holly et al. in view of Ritchie et al. fail to teach or suggest each element of amended Claim 1, but also these references fail to teach or suggest each element of Claims 2-5. As such, Claims 2-5 are also patentable over Holly et al. in view of Ritchie et al. *See* M.P.E.P. § 2143.02.

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As noted above, amended Claim 2 recites identifying an invasive microbial population of the eye, identifying an antibiotic or antifungal capable of inhibiting the proliferation of the invasive microbial population, determining the MIC and FIC values for the antibiotic or antifungal and the chelating agent; and adjusting the concentration of the antibiotic or antifungal and the chelating agent of the antimicrobial composition to inhibit the proliferation of the microbial population. Neither Holly et al. nor Ritchie et al. discloses or suggests these elements.

Because Holley et al. teaches away from the use of small molecule antibiotics or antifungals, a skilled artisan would not have an apparent reason to modify Holley et al. with the antibiotics of Ritchie et al. to arrive at the invention of amended Claim 2. *See KSR*, 127 S. Ct. at 1741.

Nor does this combination of references teach or suggest the kits of amended Claim 3 for the reasons set forth above, or the method of Claims 4 or 5 wherein the antibiotic or antifungal is an antibiotic selected from the group consisting of β-lactams, vancomycms, bacitracins, macrolides, lincosamides, chloramphenicols, tetracyclines, aminoglycosides, amphotericns, cefazolins, clindamycins, mupirocins, sulfonamides, trimethoprim, rifampicins, metronidazoles, quinolones, novobiocins, polymixins and Gramicidins, or a pharmaceutically acceptable salt thereof (Claim 4) or an antifungal selected from the group consisting of itraconazole, clomtrimazole, miconazole, natamycin, amphotericin B, cuprimycin, enilconazole, fluconazole, haloprogin, ketoconazole, nystatin and tolnaftate (Claim 5).

For at least this reason, the obviousness rejection of Claims 2- 5 is improper.

III. Conclusion.

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-5 are in condition for allowance. If any issues remain that may be expeditiously

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addressed in a telephone interview, the Examiner is encouraged to telephone the undersigned attorney at number set forth below.

Respectfully submitted,

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